Tissue Distribution/Penetration and Pharmacokinetics of CD101

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Fungal infection is an internationally neglected health topic. Over 300 million people of all ages in all countries are estimated to suffer from a serious fungal infection each year and over 1,350,000 people are estimated to die.

### Annual estimated mortality from serious fungal infection worldwide

<table>
<thead>
<tr>
<th>Fungal infection</th>
<th>Case fatality rate</th>
<th>Estimated deaths</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Cryptococcal meningitis                               | 15-20% USA  
>50% developing world | 600,000           | CDC (high) estimate                                     |
| Pneumocystis pneumonia                               | ~15% in AIDS  
~50% non-AIDS | >80,000           | Most cases in Africa not diagnosed and 100% mortality |
| Invasive aspergillosis                                | ~50% mortality in  
developed world | >100,000         | Many missed diagnoses globally                  |
| Candida bloodstream infection                         | ~40% mortality    | >120,000         |                                               |
| Chronic pulmonary aspergillosis                       | ~15% mortality in  
developed world | >450,000         | Under-diagnosed and mistaken for tuberculosis  |
| Severe asthma with fungal sensitisation (SAFS)        | <1% ?             | ~100,000 asthma  
deaths - ~50% related to SAFS | Uncertain                                         |
| Total                                                 |                    | >1,350,000       | Significant underestimate                     |

Chemical structures of echinocandin drugs

Structural modification yields advantageous chemical & biological properties
Permanent charge and highly stable ring structure

- Prolongs PK: targeting once weekly dosing
- Eliminates toxic degradation products: improved safety & dose range
- Allows high exposures: treats less susceptible pathogens
- Enables multiple formulations: systemic and topical

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2015 ICAAC Poster series: New Anti-Fungal Agents

- Preclinical Evaluation Shows CD101, a Novel Echinocandin, is Highly Stable with No Hepatotoxicity in Rats  V. Ong, et al.
- Efficacy of CD101 to Treat Echinocandin-resistant *Candida albicans* in a Murine Model of Invasive Candidiasis, Y. Zhao, et al.
• Penetration into the site of infection – key requirement for efficacy
• Factors impact tissue penetration:
  ✓ Drug factors, eg, PK properties, formulation, etc
  ✓ Host factors, eg, tissue permeability (blood-brain barrier), inflammation, etc
• Current approaches
  ✓ Tissue drug concentration – whole tissue homogenates
  ✓ Lack of spatial information → incomplete or inaccurate
• MALDI (Matrix Assisted Laser Desorption Ionization) Imaging Mass Spectrometry technology
  ✓ Powerful analytical technique for molecule localization within a tissue
  ✓ Label-free technology
  ✓ Multiplex analysis of different molecules simultaneously in the same tissue section
MALDI-mass spectrometry imaging

Dissection → Sectioning → Matrix application → Acquisition → Image reconstruction

Ion abundance

Ion quantification in regions of interest

m/z
Analytical evaluation of CD101
-spot testing by MALDI IMS

Chemical Formula: C₆₃H₈₅N₉O₁₇⁺
Exact Mass: 1225.603

10ng/ml
Immune competent invasive candidiasis mouse model

- *C. albicans* ATCC 90028 (2x10⁶ CFU) inoculated IV into 6-week-old BALB/c mice
- Single doses of CD101 at 10, 20, 40, or 60 mg/kg administered IP at 24h post-infection

**Post-dose time points:** blood (plasma) & kidneys

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Tmax (hr)</th>
<th>Cmax (µg/mL)</th>
<th>AUCₜₐₙₙ (µg⋅hr/mL)</th>
<th>AUCₜₐₙₙ/ Dose</th>
<th>Halflife (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1</td>
<td>23.1</td>
<td>736</td>
<td>73.6</td>
<td>52</td>
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<tr>
<td>20</td>
<td>6</td>
<td>43.3</td>
<td>1250</td>
<td>62.5</td>
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<td>6</td>
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<tr>
<td>60</td>
<td>12</td>
<td>95.8</td>
<td>3300</td>
<td>55</td>
<td>31.4</td>
</tr>
</tbody>
</table>
Kidney distribution of CD101 is heterogeneous. The highest drug signal is observed in the kidney medulla, with lower levels of drug reaching the outer cortex. The distribution pattern is consistent throughout all time points investigated.

Numbers are representing the number and size of fungal cell aggregates. Blinded evaluated by pathologist.
20mg/kg CD101

3h

6h

12h

48h

40mg/kg CD101

3h

12h

48h

100%

0%
CD101 Dose comparison

3h post-dose

10 mg/kg
20 mg/kg
40 mg/kg

12h post-dose

10mg/kg
20mg/kg
40mg/kg
Mouse model of Intra-abdominal candidiasis (IAC)

- *C. albicans* SC5314 (1x10⁷ CFU) + sterile stool in sterile saline (5% wt/vol mixture) inoculated IP

- Peritonitis and abscess formation (maximize at day 3 post-infection)

  Cheng S, JID 2013; 208;1529-37

- Single dose of CD101 at 20 mg/kg administered IP at day 3 post-infection
Even as tissue levels decline, drug is concentrated within the lesion after 6h post-dose.

* m/z 683.505 is Diacylglyceride 38:4
liver 6h

GMS

H&E
liver 48h

GMS

H&E
CD101 in infected mouse kidney

Images are biased to cortex region containing lesions

Like liver, tissue levels decline after 6h post-dose, but increase within lesions.
conclusions

• CD101 has superior PK properties
• Extensive tissue distribution and excellent lesion penetration
• Promising therapeutic option for intra-abdominal candidiasis
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